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Necrotizing Soft Tissue Infections
A Review

James McDermott, MD; Lillian S. Kao, MD, MS; Jessica A. Keeley, MD; Areg Grigorian, MD; Angela Neville, MD; Christian de Virgilio, MD

IMPORTANCE Necrotizing soft tissue infections (NSTIs) are severe life- and limb-threatening infections with high rates of morbidity and mortality. Unfortunately, there has been minimal improvement in outcomes over time.

OBSERVATIONS NSTIs are characterized by their heterogeneity in microbiology, risk factors, and anatomical involvement. They often present with nonspecific symptoms, leading to a high rate of delayed diagnosis. Laboratory values and imaging help increase suspicion for NSTI, though ultimately, the diagnosis is clinical. Surgical exploration is warranted when there is high suspicion for NSTI, even if the diagnosis is uncertain. Thus, it is acceptable to have a certain rate of negative exploration. Immediate empirical broad-spectrum antibiotics, further tailored based on tissue culture results, are essential and should be continued at least until surgical debridement is complete and the patient shows signs of clinical improvement. Additional research is needed to determine optimal antibiotic duration. Early surgical debridement is crucial for improved outcomes and should be performed as soon as possible, ideally within 6 hours of presentation. Subsequent debridements should be performed every 12 to 24 hours until the patient is showing signs of clinical improvement and there is no additional necrotic tissue within the wound. There are insufficient data to support the routine use of adjunct treatments such as hyperbaric oxygen therapy and intravenous immunoglobulin. However, clinicians should be aware of multiple ongoing efforts to develop more robust diagnostic and treatment strategies.

CONCLUSIONS AND RELEVANCE Given the poor outcomes associated with NSTIs, a review of clinically relevant evidence and guidelines is warranted. This review discusses diagnostic and treatment approaches to NSTI while highlighting future directions and promising developments in NSTI management.

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Author Affiliations: Department of Surgery, Stanford University, Stanford, California (McDermott); Department of Surgery, McGovern Medical School, The University of Texas Health Science Center at Houston (Kao); Department of Surgery, Harbor-UCLA Medical Center, Torrance, California (Keeley, Neville, de Virgilio); Department of Surgery, Division of Trauma, Burns, and Surgical Critical Care, University of California, Irvine (Grigorian).

Corresponding Author: Christian de Virgilio, MD, Department of Surgery, Harbor-UCLA Medical Center, 1000 W Carson St, Torrance, CA 90502 (cdevirgilio@lundquist.org).

Necrotizing soft tissue infections (NSTIs) are severe infections that present a significant risk to life and limb, characterized by the rapid destruction of soft tissue, including the skin, subcutaneous fat, fascia, or muscle. In-hospital mortality for NSTIs remains high (10%-20%), with minimal improvement over the past 20 to 30 years.[1,2] While considered rare, with a reported incidence of 3.8 to 10.3 cases per 100 000 persons annually in the United States, NSTI incidence is likely underestimated.[3] This review discusses current diagnostic and management recommendations while highlighting promising advances on the horizon.

Microbiology and Pathophysiology

NSTIs are categorized as type 1 (polymicrobial) or type 2 (monomicrobial). Type 1 is significantly more common, generally seen in older patients or immunocompromised patients with comorbidities.[4] Type 2 may affect patients of all ages and those without immunocompromise.[5] Type 2 NSTIs are commonly caused by group A *Streptococcus* or *Staphylococcus aureus* and usually affect the extremities.[6] Two additional subgroups, type 3 (*Vibrio*, *Aeromonas*, and *Clostridium*) and type 4 (fungal infections), have been proposed.[7]

The majority of NSTIs originate from bacterial infiltration after a breach in skin integrity, often due to burns, insect bites, puncture wounds, surgical incisions, or minor cuts. However, in more than 20% of cases, the cause is unknown.[8] NSTIs, particularly group A *Streptococcus* infections, may occur from transient bacteremia and hematogenous spread.[9]

The severity of illness is related to both the toxins produced by the offending pathogens and the host immune response. Toxin-mediated inflammation results in vascular thrombosis, leading to local ischemia and tissue necrosis. This fosters an environment conducive to bacterial growth and limits antibiotic delivery to the necrotic tissue.[10,11] Frequently, the inflammatory response triggered by toxins and cytokines progresses to septic shock requiring intensive care unit (ICU) admission, mechanical ventilation, and/or vasopressor support.[2]

Future Directions

Host genetics, including HLA class II haplotypes, pathogen recognition receptors, and cytokine genes, are believed to contribute to

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Table 1. Signs and Symptoms of Necrotizing Soft Tissue Infection

Sign	Percentage of patients at presentation
Classic	
Bullae	25.6
Skin necrosis	24.1
Crepitus	20.3
Gas on radiographic evaluation	24.8
Nonspecific	
Swelling	80.8
Pain or tenderness	79
Erythema	70.7
Warmth	44
Fever >37.5 °C	40
Hypotension	21.1

Table 2. Differential Diagnoses and Distinguishing Features From NSTI

Differential diagnosis	Distinguishing features from NSTI
Cellulitis	• Often not associated with hemodynamic instability, shock, or severe pain • Less associated with violaceous skin changes
Pyoderma gangrenosum	• Not associated with sepsis, fever • Associated with inflammatory bowel disease • Progresses slower than NSTI • Violaceous ulcer edges • Resistant to blunt dissection • Typically has negative blood and tissue cultures
Pyomyositis	• Characterized by abscess formation in muscles • Imaging shows focal muscle swelling and well-demarcated areas of fluid
Deep vein thrombosis	• Pain is less severe than that of NSTI • Fever may be present, though less common than in NSTI
Erysipelas	• Raised, sharply demarcated borders

Abbreviation: NSTI, necrotizing soft tissue infection.

clinical presentation and response to treatment. For example, host variations may largely explain the diversity of group A *Streptococcus* presentations, ranging from cellulitis to NSTI.[12] Genetic heterogeneity may dictate the host-pathogen interactions that contribute to differing modes of entry and immune evasion.[13] This developing understanding of pathogenesis and genomics may inform future diagnostic and treatment strategies.

Assessment and Diagnosis

Clinical Presentation and Physical Examination

NSTIs affect the extremities (57%-73%), perineum (13%-40%), trunk (13%-26%), and head and neck (2%-10%).[14] NSTIs frequently elude early diagnosis, with reported misdiagnosis rates ranging from 41% to 96%.[14] Diagnostic challenge arises partly because NSTIs often present with common nonspecific symptoms (**Table 1**) that make them difficult to differentiate from other conditions (**Table 2**).[15,16] While there are several "classic signs" of NSTI with a higher specificity, they are seen in less than half of patients.[14,17]

Concern for NSTI should be heightened in patients with comorbid risk factors, including diabetes (present in 22%-59% of cases), obesity (17%-39%), cardiovascular disease (9%-45%), peripheral arterial disease (3%-19%), intravenous drug use (2%-80%), chronic alcohol use (6%-30%), chronic liver disease (1%-4%), and immunosuppression (4%-30%).[18,19] However, up to a quarter of patients may have no underlying comorbidities.[2]

Because the diagnosis can be elusive, if a surgeon does not feel there is enough evidence to warrant exploration, serial physical examinations should be performed at least every 4 to 6 hours. Extension of erythema beyond the initial border, necrotic or violaceous skin changes, or clinical worsening should prompt surgical exploration. Detailed assessments should be documented and communicated, particularly if there is a transfer of care to another physician.

Laboratory Findings and Scoring Systems: Diagnostic Value

Wall et al[20] proposed a model to distinguish NSTIs from non-NSTIs based on a white blood cell count higher than 15 400/μL or a serum sodium level lower than 135 mmol/L. A second study added blood urea nitrogen value greater than 15 mg/dL as a further criterion.[21]

Wong and colleagues[22] subsequently developed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score that is based on 6 variables (**Table 3**). In their index study, a cutoff value of 6 points had a positive predictive value of 92% and negative predictive value of 96% in distinguishing necrotizing fasciitis from cellulitis. It should be noted that this study was specific to necrotizing fasciitis and not all NSTIs.

The LRINEC score has since been evaluated in multiple, largely retrospective studies with mixed results. Using a cutoff of 6 for diagnosing NSTI of the extremities, studies have reported a sensitivity of 49% to 75% and specificity of 83% to 85%, while a cutoff of 8 had a sensitivity of 41% and specificity of 95%.[23,24]

A recent prospective, multicenter trial proposed a new clinical risk index score, Necrotizing Soft Tissue Infections (NECROSIS), to identify NSTIs in emergency general surgery patients with skin and soft tissue infections. In a comprehensive analysis including patient demographics, admission vitals, laboratory results, physical examination, imaging, and operative findings, the authors identified 3 independent predictors for NSTI: systolic blood pressure of 120 mm Hg or less, violaceous skin, and white blood cell count greater than 15 000/μL.[25] The presence of all 3 predictors had a 100% specificity and 100% positive predictive value for both the derivation and the validation cohorts.

A prospective study showed that surgeons' suspicion for NSTI increased significantly from 43% to 86% after reviewing laboratory values, highlighting the utility of laboratory data on clinical decision-making.[17] However, the decision to proceed with surgical management should prioritize clinical assessment.

Operative Exploration to Rule Out NSTI

Given the difficulty and urgency in establishing the diagnosis of NSTI, some clinicians advocate operative exploration, even when the diagnosis is uncertain. Findings characteristic of NSTI include gray, necrotic fascia; obliteration of soft tissue planes; dishwater fluid; lack of bleeding; thrombosed vessels; lack of resistance to finger dissection in normally adherent tissue; or noncontracting muscle. In a retrospective study of 295 patients with suspected NSTI who went to the operating room, Howell et al[26] noted a 20% negative exploration rate. The authors concluded that clinicians should accept a certain negative exploration rate to avoid missing or delaying the diagnosis.

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Future Directions

Biomarker-based diagnostics are promising diagnostic adjuncts. Thrombomodulin has been shown to differentiate true NSTIs from suspected NSTIs.[27] Similarly, Rath et al[28] identified 9 biomarkers that differentiated β-hemolytic streptococcal NSTI from cellulitis: IL-1β, TNF-α, CXCL8, MMP-8, IL-6, pentraxin-3, IL-22, CCL4, and S100A8.

Metabolomic analyses may assist with diagnosis and management. In an evaluation of 97 metabolites, the abundance of 33 were significantly altered in plasma samples of patients with NSTI compared with controls without infection.[29] Metabolite-specific effects observed in vitro demonstrated their role in both bacterial growth and biofilm formation, a complicating feature that may require changes in antibiotic treatment.[29]

Laboratory Data and Scoring Systems: Prognostic Value

Small retrospective studies have identified several factors that may suggest a poor prognosis: hyperlactatemia, hyponatremia, leukocytosis, and elevated creatinine.[21,30-32] NSTI-specific scoring systems, such as LRINEC, are less accurate than non–disease-specific physiologic scores for prognostication.[33-35]

Table 3. Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score

Variable	Value	Score
White blood cell count (×10 000/μL)	<15	0
	15-25	+1
	>25	+2
Hemoglobin, g/dL	>13.5	0
	11-13.5	+1
	<11	+2
Sodium, mEq/L	≥135	0
	<135	+2
Glucose, mg/dL	≤180	0
	>180	+1
Creatinine, mg/dL	≤1.6	0
	>1.6	+2
C-reactive protein	<15 mg/dL	0
	≥15 mg/dL	+4

SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.

Future Directions

Multiple studies have attempted to identify markers of disease severity and mortality risk. Molecules such as ICAM-1, urokinase-type plasminogen activator receptor (suPAR), pentraxin-3, and fibrocolin-2 have all demonstrated potential value in NSTI prognostication.[36-38] However, perhaps the most promising potential predictor of prognosis is modeling done by machine learning. A set of 16 predictive parameters available on or before the first day of ICU care has been shown to predict 30-day mortality and outperform current scoring systems.[39] Continued developments in machine learning may yield more extensive clinical decision support systems to predict multiple outcomes.

Imaging

Multiple imaging modalities, including plain radiographs, ultrasound, computed tomography (CT), and magnetic resonance imaging have been proposed to help establish the diagnosis of NSTI but consistently fall short in their sensitivity. Given concerns that imaging may delay operative intervention, guidelines do not offer firm recommendations.[6,40-42]

Plain radiographs can detect gas in soft tissues, a finding that is specific (94%) but not sensitive (49%) for NSTIs, as gas is found in less than 25% of images.[11,14,24] Despite limited sensitivity, plain radiographs are typically used as an initial imaging step because of their accessibility.

CT is readily available at most hospitals and provides more information than plain films. It can detect air within soft tissues and other subtle signs such as fascial enhancement or edema, with a reported diagnostic sensitivity of 89% and specificity of 93%.[24] Thus, CT may serve to increase suspicion for NSTI but should only be considered when immediate exploration is not deemed necessary. Given that lack of availability may delay intervention, magnetic resonance imaging is not recommended as a diagnostic tool in patients with high suspicion for NSTI.

Ultrasound may be helpful given that it can be performed at the bedside. In a systematic review, Marks et al[43] reported that fluid accumulation along the fascial plane was the most sensitive (85.4%; 95% CI, 72.2%-93.9%), while subcutaneous emphysema was the most specific (100%; 95% CI, 92.5%-100%). Given the small number of studies, ultrasound is not yet widely used.

Future Directions

Imaging modalities that differentiate necrotic from viable tissue have yielded promising results in small studies. Indocyanine green perfusion imaging may distinguish NSTIs based on diminished fluorescence in affected tissues.[44] Thermal infrared cameras may be used to detect temperature differentials in necrotic vs viable tissue. In a study of perineal NSTIs, preoperative infrared photos correlated with resection margins in 13 of 16 patients (81%).[45] Further studies are necessary to determine if such modalities will affect the extent of debridement and clinical outcomes.

Treatment

Antimicrobial Therapy

In all cases of suspected NSTI, empirical broad-spectrum antimicrobial therapy should be initiated promptly after blood cultures. This therapy should cover Gram-positive (including methicillin-resistant *S aureus* [MRSA]), Gram-negative, and anaerobic organisms. Typically, this includes an intravenous broad-spectrum β-lactam, with adjustments based on individual patient factors. For suspected MRSA, vancomycin or linezolid should be added, and for resistant Gram-negative infections, carbapenems are recommended. Empirical therapy recommended by society guidelines can be found in **Table 4**.[6]

In unstable patients with systemic symptoms suggestive of toxic shock syndrome, clindamycin is recommended to limit exotoxin production.[6] Empirical antifungal therapy should be considered in immunocompromised patients.[46]

Antibiotic duration for NSTI varies widely because of a lack of high-quality evidence to guide recommendations.[47] There is no consensus as to whether a fixed duration is preferred over a variable

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Table 4. Empirical Antibiotics for Necrotizing Soft Tissue Infections in Patients With Normal Kidney Function

Patient status	Antibiotic combination
Stable	One of the following antibiotics: • Amoxicillin/clavulanate, 1.2/2.2 g every 8 h • Ceftriaxone, 2 g every 24 h + metronidazole, 500 mg every 8 h • Cefotaxime, 2 g every 8 h + metronidazole, 500 mg every 8 h
	Plus • Clindamycin, 600-900 mg every 8 h
Unstable	One of the following antibiotics: • Piperacillin/tazobactam, 4.5 g every 6 h • Meropenem, 1 g every 8 h • Imipenem/cilastatin, 500 mg every 6 h
	Plus One of the following antibiotics: • Linezolid, 600 mg every 12 h • Tedizolid, 200 mg every 24 h
	Or One of the following antibiotics: • Vancomycin, 25-30 mg/kg loading dose, then 15-20 mg/kg dose every 8 h • Daptomycin, 6-8 mg/kg every 24 h • Telavancin, 10 mg/kg every 24 h
	Plus • Clindamycin, 600-900 mg every 8 h

duration that is based on improvement in clinical and/or laboratory values. Several recent studies have found no differences in mortality or amputation rates with short (≤7 days) vs long (>7 days) antibiotic duration.[48,49] Prospective and retrospective studies have suggested that 48 hours of antibiotics after source control is as safe and effective as a longer course.[50,51] The Infectious Diseases Society of America (IDSA) has suggested to continue antibiotics until source control has been achieved and there is no additional evidence of systemic infection, including the absence of a fever for 48 to 72 hours.[40]

Surgery

Source control with early and aggressive surgical debridement is the most important determinant of outcome in NSTIs.[6,40] The goal of debridement is to remove all necrotic tissue so that only healthy bleeding tissue remains. Given that infection often extends beyond observed cutaneous findings, debridement beyond the area of skin changes may be required.[11] Culture and Gram stain of deep tissue should be obtained during operative debridement, including fungal cultures, to inform subsequent antibiotic therapy.[40]

Timing of Surgery

Urgent surgical debridement is necessary for optimal outcomes, yet the exact timing continues to be refined. A single-center series with 124 patients reported a relatively low mortality rate (17%), with 75% of the patients having surgery within 8.5 hours of presentation.[30] Kobayashi et al[52] found that delayed (>12 hours) surgery is associated with an increased number of surgical debridements and higher incidence of septic shock. Consistent with these series, Eastern Association for the Surgery of Trauma guidelines recommend debridement within 12 hours of suspected diagnosis. In an evaluation of 6 studies comparing patients who underwent early (<12 hours) and late (>12 hours) operative debridement, early debridement was associated with improved mortality, 14% vs 26% (P = .005).[42]

More recent joint guidelines from the World Society of Emergency Surgery, Global Alliance for Infections in Surgery (GAIS), Surgical Infection Society Europe, World Surgical Infection Society, and American Association for the Surgery of Trauma advocate for even earlier intervention, within 6 hours of admission, citing a recent meta-analysis demonstrating that surgery within this time frame offers additional mortality benefit compared with surgery after 6 hours (odds ratio, 0.43; 95% CI, 0.26-0.70; 10 studies included). The authors observed a 19% mortality rate when performed within 6 hours vs 32% when delayed more than 6 hours.[1,6] In summary, if there is high suspicion for NSTI, surgery should be performed as soon as possible, ideally within 6 hours.

Repeat Surgical Evaluation and Debridement

Current society guidelines recommend re-explorations every 12 to 24 hours after the initial operation or earlier if there are signs of disease progression or concerning laboratory results.[6] It is not uncommon for patients to require 3 to 4 operations to obtain source control.[11] In a prospective observational study, Okoye et al[53] found that repeat debridement at 24 hours compared with 48 hours after initial source control was associated with lower mortality (7% vs 33%) and less acute kidney injury (9% vs 33%).

Skin-Sparing Debridement

Skin-sparing debridement has been proposed as a less morbid alternative to en bloc resection. The approach may be suitable for cases involving only fascia, when overlying skin and subcutaneous tissue are normal. In this technique, a series of counterincisions permit the removal of subcutaneous necrotic tissue while preserving viable overlying skin.[54] The intent of a skin-sparing approach is to limit large open wounds that require skin grafting. Several authors suggest a skin-sparing approach provides equivalent source control and similar mortality rates.[54,55] However, given limited data, the decision to consider this approach should be made with caution, as the risk of inadequate debridement may lead to disease progression.

Role of Amputation

In NSTIs affecting the extremities, amputation is necessary in up to 25% of cases.[1,31] Amputation may be considered when (1) source control cannot be achieved with debridement, (2) reconstruction is unfeasible, or (3) functional status is expected to be better with amputation than reconstruction. It is important to discuss the possibility of amputation with the patient or their surrogate preoperatively.

Surgeon Specialty

At some centers, the anatomic location of NSTI may dictate surgical specialty; for example, Fournier gangrene may be primarily managed by urology. However, given the time-sensitive nature of initial debridement, surgeon availability may be more important than surgeon specialty. A small study found similar outcomes when patients with Fournier gangrene were managed by general surgery or urology services.[56]

Postoperative Wound Care

Negative pressure wound therapy (NPWT) is an adjunctive treatment that applies subatmospheric pressure to the wound surface after debridement. The optimal timing for initiating NPWT and its appropriateness for all patients with NSTIs remain unclear. Numerous studies suggest that NPWT reduces the size of the wound surface, removes exudate and residue, increases tissue

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perfusion, and stimulates granulation tissue.[57] A recent meta-analysis demonstrated that NPWT was associated with lower mortality but no difference in length of stay, number of debridements, or complication rates as compared with conventional dressings.[58]

A recent study questioned the use of NPWT in exclusively anaerobic infections, as oxygen deprivation may be less effective against these species. The authors reported that patients with anaerobic NSTIs treated with NPWT had an increased number of debridements and a higher readmission rate compared with patients with aerobic or polymicrobial infections.[59]

Given the need for frequent wound checks in the early postoperative period, it may be best to delay initiation of NPWT until the patient undergoes repeated debridements and the wound is deemed stable.

Should Patients With Suspected NSTI Be Transferred?

Given the need for complex multidisciplinary care, patients may benefit from transfer to specialized, high-volume regional centers or burn centers, which have been associated with lower mortality rates.[2,42] However, the desire to transfer must be tempered by the urgency of surgical intervention. Patients who are transferred have higher mortality rates (up to double) compared with those treated immediately at the presenting hospital.[21,60] Therefore, initial debridement should ideally occur at the first hospital, or systems for rapid transfer should be established, akin to other surgical emergencies. One such system, termed a *hub-and-spoke model*, concentrates specialized care at a hub hospital with spoke hospitals having a mechanism to expeditiously transfer their patients. This model has been shown to increase the proportion of patients who undergo debridement within the guideline-recommended time frame.[61]

Adjuncts

Hyperbaric Oxygen Therapy

Evidence supporting the clinical efficacy of hyperbaric oxygen therapy (HBOT) in NSTIs is limited to observational studies, which are prone to selection bias because critically ill patients may not be stable enough for receipt of HBOT. Two recent meta-analyses, both including nearly 50 000 patients with NSTIs, indicated significantly lower mortality with HBOT but no effect on amputation rates.[62,63] Guidelines on HBOT use in NSTIs are mixed: IDSA recommends against HBOT, while other society guidelines suggest considering it. HBOT should not delay surgical debridement nor interfere with aggressive ICU support.[6,40] Furthermore, HBOT is not readily available at many institutions. While HBOT protocols vary by institution, they usually recommend initiation with 1 to 2 sessions within 24 hours after initial debridement, followed by 1 to 2 sessions per day for several days or until no additional necrosis is observed.[63]

Intravenous Immunoglobulin Therapy

Intravenous immunoglobulin (IVIG) therapy has been used for NSTI treatment, primarily to enhance bacterial opsonization and toxin neutralization.[18] Patients with NSTI often have lower levels of protective antibodies toward key virulence factors including streptococcal pyrogenic exotoxin B and superantigens, which IVIG could potentially supplement.[64]

Box. Top 10 Key Points and Recommendations for NSTIs

Rapid diagnosis of NSTI is critical, yet differentiating it from less serious conditions such as cellulitis remains extremely challenging, as less than one-half of patients have "classic" signs on physical examination.

Laboratory values may raise suspicion for NSTI. However, a low LRINEC score does not rule out the diagnosis; clinical suspicion should take precedence over LRINEC score in the decision to proceed with surgical management.

Plain radiographs and CT scan may raise suspicion of NSTI but should neither prolong time to definitive surgical care nor deter surgery if clinical suspicion is high.

Broad-spectrum empirical antibiotics should be initiated in all patients with suspected NSTI until deep tissue cultures and sensitivities enable more targeted therapy. Antibiotics should be continued at least until surgical debridement is complete and the patient shows signs of clinical improvement. Additional research is needed to determine the optimal duration of treatment.

Transferring a patient with NSTI to a higher level of care before debridement may be associated with a higher mortality because of the inherent delays in getting the patient to the operating room.

Surgical exploration is acceptable when there is high suspicion for NSTI, even if the diagnosis is not definitively established. It is acceptable to have a certain rate of negative explorations given the importance of early intervention.

Early surgical debridement is crucial. Surgeons should strive to get the patient to the operating room within 6 hours of presentation because early debridement is associated with lower mortality.

Surgical re-exploration should be performed every 12 to 24 hours. Re-exploration should continue until the patient is showing signs of clinical improvement and it appears that no additional debridement is required.

The routine use of hyperbaric oxygen therapy is not yet recommended: more research is needed. If used, it should not interfere with surgical management or supportive care.

The routine use of IVIG therapy is not yet supported. IVIG may provide benefit in the setting of streptococcal NSTIs and toxic shock syndrome.

Abbreviations: CT, computed tomography; IVIG, intravenous immunoglobulin; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; NSTI, necrotizing soft tissue infection.

Current evidence is conflicting regarding the impact of IVIG on clinical outcomes. First, few patients receive IVIG, limiting the power of studies to detect a difference.[65] Second, observational studies may be confounded by several factors, including severity of illness and inconsistent coadministration of clindamycin. A meta-analysis of 4 observational studies and 1 randomized clinical trial (RCT) evaluating IVIG in clindamycin-treated patients with streptococcal toxic shock syndrome observed that mortality decreased from 33.7% to 15.7% with IVIG therapy.[66] A multicenter prospective study of patients with streptococcal NSTI reported improved 90-day mortality with IVIG, though shorter time to initial and subsequent surgeries may have biased the outcomes.[9] When tested in an RCT (INSTINCT trial), IVIG demonstrated no difference compared with placebo in surrogate outcomes (cytokines in the first 3 days of treatment) or in clinical outcomes (mortality, organ failure, use of life support, or 6-month quality of life).[67,68]

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Thus, although joint guidelines say IVIG can be considered, IDSA guidelines make no recommendations, recognizing the limited evidence available.[6,40]

Future Directions

As genomic, proteomic, and metabolomic data accumulate, the ability to personalize care based on genetic signatures will improve. The Improving Outcome of Necrotizing Fasciitis: Elucidation of Complex Host and Pathogen Signatures That Dictate Severity of Tissue Infection (INFECT) project is a multicenter prospective observational study that will build understanding of the pathophysiology and prognosis of NSTIs to inform diagnosis and individualized treatment.[69] Additionally, pathogen genomics remain an area of interest for vaccine development, including current preclinical and clinical evaluations of vaccines against group A *Streptococcus*.[70]

Immune modulators may offer additional future therapies for NSTIs, aimed at attenuating the inflammatory cytokine response and decreasing the incidence of persistent organ dysfunction. Reltecimod (AB-103), a CD28 T-lymphocyte receptor mimetic, inhibits T-cell activation by bacterial pathogens. A phase 3 RCT of reltecimod found significant improvements in the composite end points: alive at day 28, 3 or fewer debridements, no amputation beyond first operation, and day 14 Modified Sequential Organ Failure Assessment score of 1 or less with a point reduction of 3 or more.[71] Additional studies are needed to determine its effectiveness in clinical practice.

Prognosis

NSTIs are associated with high rates of morbidity and mortality, which are even higher among those who are socioeconomically disadvantaged. Black patients have a higher risk of complications, including a 40% increased odds of amputation, whereas Hispanic patients and patients with Medicaid or Medicare insurance have nearly a 60% increased risk of mortality compared with White or privately insured patients, respectively.[19,72] Contributors to these disparities require further exploration.

Persistent organ dysfunction after 14 days is a strong predictor of increased resource needs, unfavorable discharge outcomes, and elevated long-term mortality.[35] Outside of the acute treatment period, patients require long-term multidisciplinary support as they recover from critical illness and the consequences of aggressive surgical debridement or amputation, which are commonly associated with new challenges in daily activity and pain management.[73] Patients recovering from NSTIs report decreased health-related quality of life, particularly in the domains of decreased physical functioning, greater limitations in daily life, decreased feelings of overall health compared with others, and increased rates of depressive and/or posttraumatic stress disorders.[74,75] As knowledge about the diagnosis and treatment of NSTIs evolve, more emphasis should be placed on understanding long-term patient-reported outcomes.

Conclusions

NSTIs are a challenging spectrum of disease with limited high-quality evidence to inform best practice. Diagnosis and timely treatment rely on a high index of suspicion because physical examination findings, laboratory values, and imaging findings are rarely pathognomonic. The cornerstone of improving outcomes in NSTI is early and aggressive surgical debridement. Clinicians should be aware of the multiple promising diagnostic and treatment modalities on the horizon. Key points and recommendations are presented in the **Box**.

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